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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/291,925	04/14/1999	AVI J. ASHKENAZI	P1055R1	2757

7590 02/11/2002

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EXAMINER	
ZEMAN, ROBERT	
ART UNIT	**PAPER NUMBER**
1645	

DATE MAILED: 02/11/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/291,925	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Robert A Zeman	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14 and 16-46* is/are rejected.

7)☒ Claim(s) *15* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The request filed on 11-21-2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/291,925 is acceptable and a CPA has been established. An action on the CPA follows.

The amendment filed on 11-21-2001 is acknowledged. Claims 14, 30 and 38 have been amended. Claims 2-5, 7-13 and 23 have been canceled. Claims 14-22 and 24-46 are pending and currently under examination.

Claim Rejections Withdrawn

The rejection of claims 23 and 38 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for DNA constructs comprising a first DNA sequence encoding a precursor peptide and a second DNA sequence operably linked to the first DNA segment, wherein the second DNA sequence encodes a heterologous glycosylation site **deletion** variant, does not reasonably provide enablement for DNA constructs comprising a first DNA sequence encoding a precursor peptide and a second DNA sequence operably linked to the first DNA sequence, wherein the second DNA segment encodes a heterologous glycosylation site **addition** or any other type of glycosylation site variant is withdrawn in light of the cancellation of claim 23 and the amendment to claim 38.

The rejection of claims 2-4, 10-13 and 15 under 35 U.S.C. 103(a) as being unpatentable over Foster et al (U.S. Patent 5,641,655 IDS-5) in view of Ashkenazi et al. (PNAS Vol. 88 pages 10535-10539, 1991, IDS-5) is withdrawn. Cancellation of claims 2-4 and 10-13 and the amendment to claim 14 has rendered the rejection moot.

The rejection of claims 2-5 and 7-13 under 35 U.S.C. 103(a) as being unpatentable over Foster et al (U.S. Patent 5,641,655 IDS-5) in view of Ashkenazi et al. (PNAS Vol. 88 pages 10535-10539, 1991, IDS-5) and Rickles et al. (Journal of Biological Chemistry Vol. 263, No. 3 pages 1563-1569, 1988, IDS-5) is withdrawn. Cancellation of said claims has rendered the rejection moot.

Claim Rejections Maintained

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 34-37 and 39-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster et al (U.S. Patent 5,641,655 IDS-5) in view of Ashkenazi et al. (PNAS Vol. 88 pages

10535-10539, 1991, IDS-5) and Rickles et al. (Journal of Biological Chemistry Vol. 263, No. 3 pages 1563-1569, 1988, IDS-5) for the reasons stated in the previous Office Action in rejecting claims 2-5, 7-13, 15, 34-37 and 39-43.

Applicant argues:

1. Claim 34 is drawn to a DNA construct comprising a nucleic acid sequence encoding a mammalian t-PA prosequence operatively linked to a nucleic acid sequence that encodes a presequence other than the mammalian t-PA presequence combined with a second nucleic acid sequence encoding a heterologous glycoprotein.

2. Signal sequences include a presequence that direct protein to the ER and a prosequence that directs protein to the Golgi apparatus.

3. The cited references do not disclose all the elements of the claimed invention. Said references do not disclose or suggest the combination of a mammalian t-PA prosequence with a non-mammalian presequence.

4. The deficiencies of Foster et al. and Ashkenazi et al. are not remedied by Rickles et al.

5. Rickles et al. is directed to the isolation and purification of a cDNA encoding a murine tissue plasminogen activator. Said reference does not discuss or suggest the combination of a t-PA prosequence with a heterologous presequence.

6. There is no motivation to combine the aforementioned references.

Applicant's arguments have been fully considered and are deemed to be non-persuasive.

Applicant is reminded that the aforementioned rejection is based on the **combination** of the cited references.

As outlined in the previous Office Action, the instant claims are drawn to DNA constructs comprising a first DNA segment encoding a pro-sequence of mammalian t-PA and a second DNA segment operably linked to the first DNA segment encoding a heterologous glycoprotein (TNFR-IgG1). Foster et al. disclose DNA constructs comprising a first DNA segment encoding a secretory peptide (mammalian t-PA) joined to a second DNA segment encoding a heterologous protein (thrombopoietin). Foster et al. differs from the aforementioned claims in that the heterologous protein encoded by the second DNA segment is thrombopoietin, not TNFR-IgG1. Additionally, Foster et al. does not disclose the use of non-mammalian t-PA. Ashkenazi et al. disclose the sequence for the TNFR-IgG1. Rickles et al. disclose the sequences for and the uses of murine t-PA in the molecular cloning of complementary DNA. Since Foster et al. disclose that **t-PAs from non-human sources** can be used in their method, and even listed an example (see column 9 lines 5-9), it would have been obvious for one of skill in the art to use the sequence for TNFR-IgG1 as the second DNA segment and the non-mammalian t-PA prosequence disclosed by Rickles et al in the constructs disclosed by Foster et al. to take advantage of the increased secretion rates associated with the t-PA pro chimeras disclosed by Foster et al.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir.

1992). In this case, since Foster et al. disclose that **t-PAs from non-human sources** can be used in their method, and even listed an example (see column 9 lines 5-9) it would have been obvious for one of skill in the art to use the sequence for TNFR-IgG1 as the second DNA segment and the non-mammalian t-PA prosequence disclosed by Rickles et al in the constructs disclosed by Foster et al. to take advantage of the increased secretion rates associated with the t-PA pro chimeras disclosed by Foster et al.

Claims 14 and 16-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Foster et al (U.S. Patent 5,641,655 IDS-5) in view of Ashkenazi et al. (PNAS Vol. 88 pages 10535-10539, 1991, IDS-5) and Berman and Lasky (Trends in Biotechnology, Vol. 3, No. 2, pages 51-53, 1985, IDS-5) for the reasons stated in the previous Office Action in rejecting claims 2-4, 10-14 and 16-46.

Applicant argues:

1. Berman and Lasky do not remedy the deficiency of the references cited above.

2. Berman and Lasky is a general reference discussing expression of fully glycosylated proteins and does not discuss or suggest issues with secretion.

3. Berman and Lasky do not teach or suggest the formation of glycosylation site variants.

4. Berman and Lasky do not suggest combining a mammalian t-PA prosequence with a glycosylation site deletion variant or with a pre-sequence other than a mammalian t-PA pre-sequence.

Applicant's arguments have been fully considered and are deemed to be non-persuasive. Again, Applicant is reminded that the aforementioned rejection is based on the **combination** of

the cited references. As outlined in the previous Office Action, Foster et al. disclose DNA constructs comprising a first DNA segment encoding a secretory peptide (mammalian t-PA) joined to a second DNA segment encoding a heterologous protein (thrombopoietin). The disclosure by Foster et al. differs from the aforementioned claims in that the heterologous protein encoded by the second DNA segment is thrombopoietin, not TNFR-IgG1. Additionally, Foster et al. does not disclose the use of glycosylation site variants as the products of the second DNA fragments. Ashkenazi et al. not only discloses the sequence for the TNFR-IgG1, but also potential asparagine-linked (N-linked) glycosylation sites (see Figure 1 on page 10536). Since, as disclosed by Berman and Lasky, N-linked glycosylation plays a role in the solubility half-life and antigenicity of the glycoprotein, it would have been obvious for one of skill in the art to alter the codons for the potential N-linked glycosylation sites in the sequence for TNFR-IgG1 (disclosed by Ashkenazi et al.) and use the resulting sequences as the second DNA segment in the constructs disclosed by Foster et al. The use of the aforementioned "TNFR-IgG1 glycosylation variants" would not only take advantage of the increased secretion rates associated with the t-PA pro chimeras disclosed by Foster et al. but would allow for the rapid development of recombinant TNFR-IgG1 protein with tailored solubility, half-life and antigenicity properties.

New Claim Objections

Claim 24 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the

claim(s) in independent form. Claim 24 is recites as its sole limitation "is a glycosylation site deletion variant". This is a limitation of the parent claim (claim 14) as amended in Paper No 22.

Conclusion

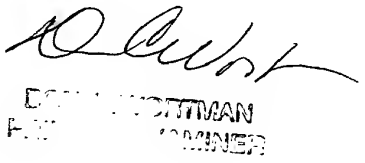
Claim 14 and 16-43 are rejected.

Claim 15 is free of the art of record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A Zeman whose telephone number is (703) 308-7991. The examiner can normally be reached on M-Th 7:30 am - 5:00 pm and Alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Donna Wortman can be reached on (703) 308-1032. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Robert A. Zeman
January 30, 2002